REMARKS

Claims 1 through 18 and 20-25, where claims 5 and 7-10 are as amended above and claims 21-25 are new, are pending following the entry of this Amendment. Claims 1, 5, 7, 10 and 17 are independent claims.

Amendment of Objected Claims

Initially, Applicant is pleased to note that claims 7 and 10-13 were not rejected, but rather, were objected to. Although the basis for the objection was not stated in the Office Action, it is believed that the objection was that they depended ultimately from previously presented independent claim 5, which was rejected.

To overcome the understood basis for the objection, claims 7 and 10 have been amended to be independent claims, incorporating the subject matter of claim 5 prior to the amendment of claim 5 herein. Similarly, to help keep the claims in order, claims 8 and 9 were amended to depend from claim 7, rather than from claim 5, and new claims 21 and 22 were added that correspond to original claims 8 and 9 and that depend from now-amended claim 5. No new matter was added in any of these amendments or new claims. Entry of these amendments to claims 7-10, and reconsideration and withdrawal of this objection are respectfully solicited. It is believed that claims 7-13 are now in condition for allowance.

Amendment of the Abstract

The Abstract was objected to as not reciting that the radiation being treated is ionizing radiation. The Abstract has been duly amended as supported by page 10, second paragraph. Entry of the amended Abstract and reconsideration and withdrawal of this objection are respectfully solicited.

Summary of Remaining Claims

Independent claim 1 and its dependent claims 2-4, 14 and 20, are directed to a treatment of a subject following exposure to ionizing radiation, by administering a compound of formula I, other than mesna.

Independent claim 5, which has been amended as explained below, and its dependent claims 6, 15, 16, 21 and 22, are directed to a prophylactic treatment by intravenous or oral administration of a compound of formula I, other than mesna.

Independent claim 5, reciting prophylactic intravenous or oral administration to a subject prior to exposure to ionizing radiation, has been amended to indicate that the claim does not include mesna among the formula I compounds being administered. Claim 5 has also been amended to recite that the administration is at a time prior to the subject's exposure effective to provide the prophylactic protection. Clearly, if the administration is too early, no prophylactic effect would be possible. This amendment is supported in several locations throughout the application, such as the first paragraph at page 1, at page 10, lines 12-16, at page 12, lines 15-17, and at page 13, lines 3-8. No new matter has been added by this amendment, and the entry of amended claim 5 is respectfully requested.

Independent claim 17, and its dependent claims 18 and 23-25, are directed to a method of protecting against ionizing radiation, including post-radiation exposure, by administering a compound of formula I other than mesna. New claims 23 and 24 correspond to claims 8 and 9, relating to intravenous and oral administration, respectively, and claim 25 corresponds to claim 14, relating to preferred compounds not disclosed or suggested in the cited references.

Summary of Patentability of Claims to Treatment Following Exposure to Ionizing Radiation

Claims 1-4, 14 and 20 specifically claim post-exposure treatment. Claims 17, 18 and 23-25 also cover post-exposure treatment. The cited prior art, alone or together, simply does not teach or suggest anything about the use even of mesna, or its effectiveness or even its potential effectiveness in treating subjects which have already been exposed to ionizing radiation to protect them against the adverse effects of such ionizing radiation. To the extent that the cited references may disclose use of mesna prior to a subject's ionizing radiation, a point discussed more fully below, and even accepting only for the sake of argument that mesna is fairly disclosed prior to exposure, such a disclosure would not indicate to anyone skilled in the art that mesna could be or should be applied post-exposure, or if it were to be applied, that it would in any way be effective.

Summary of Patentability of Claims Directed to Treatment with a Compound Other Than Mesna

Claims 5, 6, 15, 16, 21 and 22, and claims 17, 18 and 23-25 all specifically claim the use of a compound of formula I other than mesna. Thus, these claims include dimesna, among other compounds, and claims 15 and 25 specifically cover compounds other than sulfhydryl compounds (compounds where R_1 is other than H), such as thiols (where R_1 is lower alkyl), disulfides (including dimesna) and conjugates with amino acids. As pointed out in more detail below, mesna and dimesna exhibit entirely different physiochemical properties and behaviors. Thus, dimesna and the other non-mesna compounds that are not disclosed or suggested in the cited prior art would not be obvious candidates, even to try, and even ignoring the lack of any suggestion of their effectiveness in the prior art.

Due to the differences mentioned in the above summaries alone, Applicant respectfully submits that the claims pending after entry of the foregoing amendments define a patentable invention and are in condition for allowance.

Distinctions Between Dimesna and Mesna

The Applicant would like to respectfully remind the Examiner of the fact that dimesna (Tavocept®; BNP7787) and mesna exhibit entirely different chemical, biochemical, pharmacological, and toxicological properties and behavior. A number of these differences are set forth below, in tabular form, for the Examiner's convenience.

i) Dimesna predominates as disulfide in plasma; whereas mesna is found as a disulfide in concentrations of < 3% in plasma;

ii) Thiols and disulfides obey a law of mass action relationship in plasma and cells, the free thiol hypothesis (confirmed in non-clinical, animal and human studies);

iii) Dimesna is non-toxic relative to its free thiol metabolite (mesna);

iv) Mesna interferes with cisplatin anti-tumor activity; whereas dimesna does not;

v) Greatly reduced reactivity of dimesna relative to cystine (most abundant), glutathione, and mesna;

vi) Non-enzymatic thiol transfer (SN_2 displacement) is primary metabolic route for dimesna (and physiological disulfides/thiols)

vii) Dimesna modulates taxane/epothilone/GTP tubulin hyperpolymerization;

viii) Mesna has no effect on tubulin polymerization;

ix) Mesna is ***not*** rapidly oxidized to dimesna in plasma; major product is mixed disulfides (limitations of HPLC analytical methods using indirect measurement);

x) Dimesna uptake limited primarily to kidney (epithelial cells lining tubular brush border), intestines, bone marrow, and (probably) DRG; 0 to < 5% uptake in tumor cells; distribution and metabolism is key for toxicity prevention.

Detailed Explanation of Non-Obviousness of the Claimed Invention in Response to the Office Action

Claims 1-6, 8, 9 and 14-20 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Plowman et al. letter in *Lancet*, January 17, 1987, page 167, ("Plowman") in view of *Drug Facts and Comparisons*, 1994, p. 2841 ("*Drug Facts*"). The Office Action indicated that Plowman teaches the parenteral administration of mesna of a compound of formula I to provide radioprotection at a dose of 400 mg/kg, and that Plowman was motivated to administer mesna based on structural considerations, i.e., its sulfhydryl group. The Office Action also pointed out that in the disclosed mouse model, half of the mice were given the median (known) lethal dose, 400 mg/kg 20 minutes before total body irradiation ("TBI"). The

Office Action acknowledged that Plowman fails to discuss administration of other sulfhydryl containing compounds, such as dimesna, or other dosing regimens, but indicated that Plowman suggests optimal routes of administration, optimal dosing regimens and optimal doses of mesna require further study.

The Office Action characterized *Drug Facts* as teaching both intravenous and oral administration of mesna with a recommended clinical dose of 0.24 g/m^2 with an intravenous dosage range of 0.8 to 1.6 g/m^2, and that *Drug Facts* discloses that the pharmacologically active mesna is oxidized to the disulfide dimesna when exposed to oxygen.

In the last two lines of page 3 and in lines 1, 2 and 4 of page 4 of the Office Action, the following statements are made:

> After oral administration, mesna and dimesna are both absorbed from the intestine, and dimesna undergoes reduction to mesna during intestinal absorption. When present in plasma, mesna oxidizes to dimesna....Dimesna is converted to mesna during intestinal absorption.

Based on the above-quoted statements, the Office Action concludes that in view of the combined teachings of the prior art, the skilled artisan would have been motivated to administer mesna for its known radio protective properties, and the dosages of claims 2, 6 and 20 overlap with those established clinically, and further, that both oral and parenteral administration is known in the prior art. Finally concerning this basis for the rejection of these claims, the Office Action indicates that Plowman provides clear motivation to seek optimal dosing regimens.

Applicant respectfully traverses this rejection on the following grounds.

At best, and out of context with the rest of his short letter to the *Lancet*, Plowman discloses 10% radioprotection when mesna was administered to more than 100 mice intraperitoneally at a dosage of 400 mg/kg 20 minutes before the mice were subjected to a median lethal dose of TBI. What the Office Action failed to consider is that in Plowman, mesna was not administered to provide radioprotection. Rather, mesna was administered with cyclophosphamide prior to TBI to be followed by bone marrow transplantation (BMT), where the mesna was used to counteract toxic effects on the bladder of the cyclophosphamide. Instead of using mesna as a radio protector prophylactically to overcome adverse consequences of ionizing radiation therapy or post-exposure to treat for any adverse effects of ionizing radiation, Plowman specifically warns **against** using mesna too close to TBI with the following words:

> Unless our further work reveals differential radioprotection, this drug should not be present at the time of TBI. Mesna has a short half-life (2h) and the policy adopted by this hospital is to allow at least 12 h to elapse between cessation of mesna infusion and TBI. [Emphasis added.]

As a result of this warning, one skilled in the art would not use mesna as a radio protector prophylactically to overcome adverse effects of ionizing radiation. There is no teaching or suggestion in Plowman that mesna should positively be used to protect against the adverse effects of ionizing radiation, as claimed in the present application. In contrast, relying on Plowman, those skilled in the art would not use mesna when it could affect TBI, as TBI is presented as a desirable treatment without any mention of any adverse effects of TBI, since they and Plowman do not want TBI to be affected by mesna. When a reference teaches away from a claimed invention, as is the case here, it is a very strong indication of non-obviousness, and cannot reasonably support an obviousness determination.

Claims 1-4, 14 and 20 are directed only to post-radiation exposure treatment using a compound of formula I, which is not disclosed or suggested in the cited references. One skilled in the art would not reasonably expect that a compound of formula I, administered after the subject is exposed to the ionizing radiation, would be effective in overcoming adverse effects of the ionizing radiation to which the subject was previously exposed. This is true even assuming only for the sake of argument that Plowman and *Drug Facts* together disclose administration of mesna for radio protective purposes prior to subjecting the subject to radiation, a position with which Applicant strongly disagrees, as explained herein.

Plowman also does not render obvious, alone or in combination with *Drug Facts*, claims 5, 6, 15, 16, 21 and 22, where independent claim 5 is directed to use of a compound of formula I, other than mesna, which is administered intravenously or orally (not intraperitoneally, as taught in Plowman) in an amount and at a time effective to prophylactically protect against adverse ionizing radiation effects.

The reasoning mentioned above concerning claim 5 and its dependent claims also applies to independent claim 17, and its dependent claims 18 and 23-25, since claim 17 also excludes mesna.

Additionally, with reference to other aspects of the obviousness rejection, Applicant cannot find any support in the cited references for the above-quoted statements. Support for the

statement: "After oral administration, mesna and dimesna are both absorbed from the intestine," cannot be located. Applicant is not aware of any quantitative studies on bioavailability of orally administered mesna or dimesna in a human gastro-intestinal tract. The only information known to Applicant relating to oral administration along these lines concerns the presence of these compounds in rat kidneys. Therefore, without understanding the basis for this quoted statement in the Office Action, Applicant respectfully declines to accept as accurate the statement that mesna or dimesna is absorbed from the intestine.

Further, Applicant, who is also an inventor in Hausheer et al. U.S. Patent 5,789,000 ("Hausheer"), cited to the USPTO and acknowledged in an attachment to the outstanding Office Action, respectfully refuted in this prior patent the statements "dimesna undergoes reduction to mesna during intestinal absorption;" "when present in plasma, mesna oxidizes to dimesna;" and "dimesna is converted to mesna during intestinal absorption." Hausheer explains in significant detail with reference to Fig. 1A (referred to in Hausheer as the "Old Hypothesis Left-hand Column"), Fig. 1B (referred to in Hausheer as "New Hypothesis Middle Column) and Fig. 1C (referred to in Hausheer as "New Hypothesis Right-hand Column"), how and why mesna is not oxidized to dimesna (Fig. 1A), but rather, enters cells as a mesna-thiol amino acid conjugate (Fig. 1B). Hausheer also explains that dimesna does not undergo reduction to mesna in plasma, but rather, maintains its dimer form. Dimesna has a different mechanism than mesna, which may be one reason why dimesna has a significantly better toxicity profile than mesna (see the paragraph bridging pages 4 and 5 of the present application). Please see Hausheer at column 3, line 29, to column 6, line 3. Since the above-described quoted statements found within the Office Action have been refuted as described in this paragraph, Applicant respectfully submits that they are not appropriate for use as a basis to support an obviousness conclusion.

The next issue concerns the Office Action's indication that Plowman suggests that optimal routes of administration, optimal dosing regimens and optimal doses of mesna require further study, with apparent reference to the following statement in Plowman: "We are now looking at the route of administration and the time and dose of mesna in respect of the radioprotection achieved." The point that Plowman may have been studying or researching other routes of administration than intraperitoneal and other dosages besides 400 mg/kg in mice, without ever reporting what was done or any results of such studies (if they even were ever carried out or completed) does not render Applicant's claimed invention obvious. At best,

Plowman's disclosure is an inconclusive invitation to try to determine other routes of administration and dosages, but this is not the appropriate test for an obviousness determination. The very lack of any further reports by Plowman or any others since 1987 for the use of mesna as a radio protector, let alone any other compound within formula I, such as dimesna, or any other reports of dosage or treatment regimens are strong, objective indicators of non-obviousness. Certainly, in all of this time, if Plowman or anyone other than Applicant thought of such use for mesna or other compounds within formula I, it would have been reported and cited in the Office Action.

Drug Facts adds nothing to the inadequate disclosure of Plowman. Even though *Drug Facts* discloses oral and intravenous administration of mesna, such administration is not at all associated with any radio protective use of mesna whatsoever. To the contrary, *Drug Facts* merely discloses intravenous bolus administration of mesna for "the prophylaxis of ifosfamide-induced hemorrhagic cystitis." No other use is provided for oral dosage forms of mesna. It is too much of a leap to assume that intravenous or oral administration of mesna as suggested by *Drug Facts* for overcoming the toxic effects of ifosfamide and other toxic chemotherapeutic agents would be effective to provide prophylactic or post-exposure effective treatment for ionizing radiation exposure. The Applicant respectfully submits that to overlay the *Drug Facts* routes of administration and dosages onto Plowman's disclosure would be inappropriate hindsight reconstruction based upon Applicant's own disclosure.

Regarding the Office Action's indication that *Drug Facts* discloses that when mesna is exposed to oxygen, mesna is oxidized to the disulfide, dimesna, the Office Action left out any recognition of the very next sentence in *Drug Facts*: "As a result, any unused drug remaining in the amps after dosing should be discarded and a new amp used for each administration." One skilled in the art could hardly be expected to interpret this as a direction or even a hint to use dimesna instead of mesna, even for the other uses of *Drug Facts*. The opposite message is unmistakably clear: do not use dimesna – throw it away!

Rather than evidencing a motivation to combine the disclosures of Plowman and Drug Facts, an objective review reveals the opposite conclusion – they are not reasonably combinable, and even if they were, they do not render the present invention unpatentable.

The cited references do not disclose or suggest post-radiation exposure treatment as claimed in claims 1-4, 14 and 20; a prophylactic treatment by intravenous or oral administration

of a compound of formula I other than mesna as claimed in claims 5, 6, 15, 16, 21 and 22; or a method of protecting against ionizing radiation, including post-radiation exposure, by administering a compound of formula I other than mesna as claimed in claims 17, 18 and 23-25. The cited references fail to fairly teach or suggest either the claimed timing or route of administration or the claimed compound of formula I (sometimes not even including mesna). Accordingly, the cited prior art does not render the presently claimed invention unpatentable.

Since all of the objections and rejections have been overcome, reconsideration and withdrawal of all objections and rejections and an early Notice of Allowance are respectfully solicited.

The Examiner is invited to contact the undersigned attorney by telephone if a discussion would advance the prosecution of this application.

Respectfully submitted,

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March 3, 2006 By: _____
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